Relationship between Severe Asthma and Nasal Polyps

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Chronic rhinosinusitis is a common disease worldwide and can be categorized into chronic rhinosinusitis with nasal polyps and chronic rhinosinusitis without nasal polyps. Chronic rhinosinusitis with nasal polyps is common in patients with asthma and, particularly, severe asthma. Severe asthma is effectively treated with biologics and the coexistence of severe asthma with chronic rhinosinusitis with nasal polyps presents a phenotype that is more likely to respond to such treatment.

Keywords: asthma ; chronic rhinosinusitis with nasal polyps (CRSwNP) ; Severe asthma ; IL-5 ; IL-4 ; IL-13 ; IgE

1. Introduction

The prevalence of chronic rhinosinusitis is around 10% in the US and Europe [1]. Chronic rhinosinusitis can be categorized into two phenotypes: chronic rhinosinusitis with nasal polyps (CRSwNP) and chronic rhinosinusitis without nasal polyps (CRSnNP) [2]. CRSwNP is a chronic inflammatory disease of the nasal passage linings or sinuses leading to soft tissue growth, known as nasal polyps, in the upper nasal cavity [3]. Symptoms experienced by patients with nasal polyposis include nasal blockage, loss of smell, rhinorrhea, sleeping difficulties and impairments in social, emotional and lifestyle well-being but also symptoms derived from lower airway involvement [4][5].

Current treatment options for patients with nasal polyposis (NP) are intranasal and, for severe cases, oral corticosteroids (OCS) and long-term antibiotics [3][6]. Surgery to remove the polyp tissue may also be indicated for severe cases [7]. However, polyps have a strong tendency to recur, often leading to the need for repeated surgery. Recently, monoclonal antibodies (mAbs) have been implemented in the treatment of difficult-to-treat CRSwNP, targeting specific molecules that are implicated in the inflammatory process, in an effort to relieve patients, not only from their symptoms but also, from the burden of OCS and their numerous side effects. The biologics that have been approved are omalizumab, mepolizumab and dupilumab [8].

Patients with CRSwNP have a Th2-predominant type of inflammation and present high levels of interleukin-5 (IL-5) and eosinophilic inflammation, an image that is often also seen in severe asthma, where the aforementioned mAbs are also used with great efficacy [9][10]. However, NP is not characterized by high production of IL-5 and eosinophilia in all patients. Asthma, and especially severe asthma, is associated with various comorbidities and NP is one of the most frequent [11][12]. Asthma affects around 4.3% of people worldwide, with its prevalence reaching up to 10% in the United States [13]. Although most asthmatics have a benign level of the disease, around 5% suffer from severe asthma, with many exacerbations, impaired lung function, worse quality of life and repeated use of OCS [14]. The most common endotype of severe is asthma is the Th2 high type, with eosinophils being pivotal in the development of airway inflammation [15]. Chronic rhinosinusitis with nasal polyposis affects around 40% to 60% of severe eosinophilic asthma [16][17][18][19]. Therefore, it is of great interest to further elucidate the link between severe asthma and CRSwNP, especially since their coexistence can be managed with the use of the same mAbs.

2. The Link between Severe Asthma and Nasal Polyps

The association between asthma and CRSwNP is not just a simple coexistence. Core underlying pathophysiological mechanisms are shared between them, with T2 inflammation being the cornerstone of both airway disorders. Thus, taking into account that the extent of T2 inflammation strongly impacts the severity of both diseases, it can be expected that patients suffering from severe asthma will usually experience severe CRSwNP symptoms too, and vice versa [20]. Around one out of two patients with CRSwNP have some form of lower airway disease, and the more severe asthma becomes, the more likely is a patient will have nasal polyposis [21].

T2-high inflammation results from two different molecular pathways, eventually leading to the production of cytokines such as interleukin-4 (IL-4), interleukin-5 (IL-5) and interleukin-13 (IL-13), which in turn orchestrate the production, migration and tissue infiltration of eosinophils and mast cells. The first pathway revolves around the adaptive immune response

through the stimulation of T-helper 2 (T_H2) $CD4^+$ cells by antigen presentation. The second pathway revolves around the innate immune response since the type 2 innate lymphoid cells (ILC2) are triggered by alarmins such as thymic stromal lymphopoietin (TSLP), interleukin-25 (IL-25) and interleukin-33 (IL-33). These alarmins act exactly as their name suggests, by “raising the alarm” of innate immunity after the exposure of airway epithelium to environmental triggers such as allergens or viruses [15].

The most common cause of asthma exacerbation is viral infections [22]. Accordingly, it is no surprise that asthma is more likely to exacerbate and is harder to control in patients with CRSwNP [23]. One of the hallmarks of nasal polyposis is epithelial barrier dysfunction since the expression of tight junction and cell adhesion proteins is significantly thwarted, compared to healthy individuals, as a direct result of IL-5 on airway epithelial cells expressing the IL-5 receptor (IL-5R) [24] [25]. The weakened epithelium acts like fertile soil to facilitate the alteration of the local microbiome of the sinonasal mucosa, eventually leading to persistent inflammation [1]. The compromised immune response of patients with CRSwNP is evident since they are more easily colonized by bacteria such as *Staphylococcus Aureus* and are also more prone to viral infections, which further activate the previously mentioned adaptive and immune response systems, acting like kindling in the flame of T2 inflammation [26]. Moreover, the Th1/Th17 response, which is essential in the defense of the host to viral infections, is dysregulated in T2-high inflammatory diseases and instead, T2 biomarkers are increased after exposure to viruses such as eosinophils, IL-4, IL-5 and IL-13 in nasal fluids and bronchoalveolar lavage (BAL) [27]. This aberrant T2 response to viral infections and the presence of T2 cytokines in turn leads to a less potent production of type I interferons which normally have anti-viral effects [28]. This immune dysregulation can also explain the finding of increased viral replication in asthmatics compared to healthy subjects in an in vivo study following experimental rhinovirus infection [27].

Growing evidence is showing that CRSwNP, especially in association with severe asthma, is also linked to mucus plugs and bronchiectasis. As many as 45% of patients with bronchiectasis have been diagnosed with CRSwNP. On the other hand, bronchiectasis is more common in patients with CRSwNP compared to asthmatics [29]. This corroborates the hypothesis of the “united airways diseases”, which in the context of T2-high inflammation, highlights the role of eosinophils and IL-5 in promoting and sustaining upper and lower airways manifestation. The presence of bronchiectasis along with severe asthma has been linked with more frequent exacerbations, possibly in the context of a more prone-to-infections respiratory system due to the presence of bronchiectasis [30]. There is even the possibility that T2-high inflammation is the actual cause that leads to bronchiectasis development in the first place and the real overlap of diseases such as severe asthma, CRSwNP and bronchiectasis may be much higher than estimated. These findings suggest that in newly diagnosed patients with severe asthma, especially if it coexists with CRSwNP or needs high OCS doses to maintain control, a high-resolution computed tomography (HRCT) of the lungs is an almost mandatory step. Consequently, experts can personalize treatment based on existing comorbidities before initiating treatment with an mAb CT score and ameliorate patient outcomes. [31].

A distinct phenotype of coexisting asthma and nasal polyposis is aspirin-exacerbated respiratory disease (AERD). It is marked by CRSwNP, difficult-to-control asthma and adverse respiratory reactions to medications such as aspirin or non-steroid anti-inflammatory drugs (NSAIDs) which inhibit cyclooxygenase-1 (COX-1) [32]. Eosinophils and mast cells play a detrimental role in AERD pathophysiology by releasing inflammatory mediators, though unlike asthma where eosinophils are in the spotlight, mast cells are thought to play a more important role in the pathogenesis of CRSwNP by secreting numerous pro-inflammatory molecules. The most prominent are prostaglandin D2 (PGD_2), prostaglandin F2alpha ($PGF_{2\alpha}$) and cysteinyl leukotrienes such as LTE_4 [33][34].

PGD_2 is an inflammatory mediator which can bind to the chemoattractant receptor-homologous molecule (CRTH2) found on the surface of T_H2 cells, ILC2, eosinophils and basophils, activating and recruiting them to the airways. Additionally, it can bind to the DP1 receptor, also leading to chemotaxis of pro-inflammatory cells and causing nasal edema by inducing vasodilation [33]. $PGF_{2\alpha}$ is another eicosanoid produced by eosinophils, mast cells and possibly epithelial cells of the respiratory tract. It also acts as an agonist for the CRTH2 receptor [35]. Furthermore, it has been known for almost 50 years that inhalation of $PGF_{2\alpha}$ can induce bronchoconstriction even in healthy individuals, but asthmatics are far more sensitive and respond with more severe flow impairment, implying that in patients with comorbid CRSwNP and bronchial asthma the excess production of $PGF_{2\alpha}$ can worsen the symptoms of asthma [36]. Last but not least, LTE_4 is another eicosanoid product which is produced mainly from eosinophils and mast cells. IL-5 plays a crucial role in regulating its production since inhibition of IL-5 signal through anti-IL-5 or anti-IL-5R biologics drastically reduces its levels. LTE_4, in turn, can upregulate the production of PGD_2 and $PGF_{2\alpha}$, therefore inhibition of IL-5 acts beneficially for two crucial inflammatory mediators [37][38].

IL-5, as previously mentioned, is the most crucial cytokine in the pathogenesis of T2-high inflammation. Its effect is not limited to asthma since it can also induce the production of pro-inflammatory eicosanoids associated with AERD. In patients with AERD, the expression of IL-5R on the surface of eosinophils and mast cells is substantially increased, facilitating the T2 signaling process [39]. Additionally, IL-5 has recently been implicated in the process of weaking the epithelial barrier among airway epithelial cells (AEC). AEC have a fully functional IL-5R on their surface and it is plausible to discuss whether the concentration of IL-5 can affect the cell-to-cell adhesion of AEC [24]. For all these reasons, blocking IL-5 signaling is currently the most dominant weapon in combatting T2-high inflammation. An indirect marker of success for anti-IL-5 treatment is the higher expression of the CRTH2 receptor on the surface of eosinophils and basophils. Since deprivation of IL-5 reduces the levels of all three aforementioned eicosanoids, the receptor remains on the surface of the granulocytes instead of being internalized to proceed with molecular signaling [35][40][41].

IgE is the oldest target of biologic agents for asthma, with almost 20 years of experience with the anti-IgE mAb omalizumab. The role of IgE is also important in the coexistence of asthma and nasal polyps, especially in an allergic background, for instance, in patients with aeroallergen sensitization or other microbial antigens [42]. It is also considered a prominent T2 inflammation biomarker since elevated levels of IgE can increase the inflammatory response from mast cells and basophils. The ultimate goal of anti-IgE treatment is to reduce the binding of basophils with IgE and eventually replace them with new basophils, which will not be sensitized by IgE and thus not driven into an aberrant inflammatory response. The same applies for lung mast cells, which, if not sensitized by IgE, do not degranulate and do not promote allergic reactions [43]. Additionally, not only do the serum levels of IgE positively correlate with the severity of mucosal disease in patients with asthma and nasal CRSwNP, but elevated levels of IgE in sinonasal tissue is also a marker of a higher disease burden, highlighting its key role [44][45]. The role of IgE in eosinophilic centered inflammation is not yet elucidated, however, literature suggests that preventing the binding between IgE and the CD23 receptor on B-cells can halt the production of IL-5 and, therefore, subside the T2 inflammatory cascade around eosinophils [46].

It is clear that the link between these two respiratory disorders is strong, and in the era of personalized medicine, health experts should aim to optimize treatment for both asthma and CRSwNP. The shared molecular pathway of T2 inflammation is beneficial for targeted therapy with mAbs against pivotal cytokines, such as IL-4, IL-5 and IL-13 in both diseases. Initial results have shown remarkable success, and as the arsenal is growing, it is tempting to endotype asthma and CRSwNP when they coexist in order to choose the right biologic agent not for one, but for two health conditions, simultaneously. In the near future, researchers may even be in a position to target T2 inflammation in multiple steps with a combination of biologics, although, at the moment, no trials have been designed to test this hypothesis.

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